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(12) # EUROPEAN PATENT APPLICATION

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(54) **Pharmaceutical formulation comprising beta-lactam antibiotics.**

(57) Extrudable water-dispersible composition comprising amoxycillin trihydrate and potassium clavulanate together with conventional excipients and a non-hygroscopic water soluble binder.

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Croydon Printing Company Ltd.

PHARMACEUTICAL FORMULATION

The present invention relates to pharmaceutical compositions for oral administration in the treatment of bacterial infections.

West German OLS No 28 43 318 discloses pharmaceutical compositions suitable for oral administration which comprise 20 mg to 1500 mg of amoxycillin trihydrate, 20 mg to 500 mg of potassium clavulanate and a pharmaceutically acceptable carrier with the proviso that the weight ratio of amoxycillin trihydrate to potassium clavulanate is from 6:1 to 1:1.

It has now been found that pharmaceutical compositions comprising amoxycillin trihydrate and potassium clavulanate may be prepared in the form of an extrudate suitable for direct ingestion or dispersion in water prior to ingestion.

Accordingly, the present invention provides an extrudable water-dispersible composition comprising amoxycillin trihydrate and potassium clavulanate together with conventional excipients and a non-hygroscopic water soluble binder.

Suitably the weight ratio of amoxycillin to clavulanic acid in the pharmaceutical composition of the present invention is from 12:1 to 2:1, for example 8:1, 6:1, 5:1, 4:1, 3:1 or 2:1. Preferred weight ratios of amoxycillin to clavulanic acid are 8:1, 4:1 and 2:1.

Suitable conventional excipients include flavouring agents, preservatives and colouring agents. The materials present in such compositions should have low free moisture contents and preferably be pre-dried; advantageously an edible desiccant may be incorporated in the composition. Tightly bound water, such as water of crystallisation normally has little adverse effect on stability.

The water soluble non-hygroscopic binder is suitably soluble in organic solvent and is suitably an organic polymer. Preferred water soluble non-hygroscopic binders include hydroxypropylmethylcellulose and polyvinylpyrrolidone/polyvinylacetate copolymer, and hydroxypropylcellulose.

The organic solvent in which the non-hygroscopic binder is soluble may be any pharmaceutically acceptable inert solvent for the binder which is sufficiently volatile to be readily removed from the extrudate. Examples of such solvents include methanol, ethanol, n- and iso- propanol, chloroform, methylene chloride, acetone, methylethylketone, methyl acetate, ethyl acetate, trichloroethylene, tetrachloroethylene, carbon tetrachloride or like solvents or homogeneous mixtures of such solvents.

Also included within the scope of the present invention is a process for the preparation of an extrudable water-dispersible composition as hereinbefore described which comprises bringing into association the components of said composition and thereafter extruding the blended mixture.

It is preferable that the formulation of the composition is carried out in a dry atmosphere, eg one containing less than 40% relative humidity and preferably one containing less than 30% relative humidity.

After the preparation of the extrudate it will normally be seived to remove any particles present of undesirable proportions. Optionally an edible desiccant material may be dusted onto the extrudate.

The extrudate may be administered orally either in the dry form, or as a reconstituted syrup. The syrup may be formed from the extrudate in the usual way, for example by agitating the extrudate in a suitable solvent, such as water, together with conventional syrup additives if so desired. The composition may be presented for example in protective packages such as screw cap bottles or aluminium foil sachets containing multiple doses, or in single dose sachets.

The weight of extrudate in a single dose will depend on factors such as the actual ratio of amoxycillin trihydrate and potassium clavulanateused, and the nature of the bacterial infection being treated, and will be a weight suitable for the intended mode of administration. Normally, for example, between 0.25 - 10 g more suitably 0.5-5 g of the extrudate will comprise a single dose.

The weight of amoxycillin trihydrate and potassium clavulanate in a single dose of the extrudate will be such that the single dose contains sufficient amoxycillin trihydrate and potassium clavulanate for effective treatment of the infection. The single dose will be repeated according to the usual dosage regime for amoxycillin trihydrate and potassium clavulanate compositions.

The invention also provides a method of treatment of bacterial infections in man, which method comprises the oral administration to the sufferer of an effective amount of amoxycillin trihydrate and potassium clavulanate in the form of the extrudate of the invention.

In the following Examples, which illustrate the invention, the compositions were formulated under a dry atmosphere.

Example 1

Extruded granules of the following composition were prepared:

INGREDIENTS	mg PER UNIT DOSE	%
Amoxycillin Trihydrate BP equivalent to amoxycillin	136.50	13.650
Potassium Clavulanate equivalent to clavulanic acid	70.00	7.000
Silicic acid, anhydrous (Syloid ALI)	50.00	5.000
Hydroxypropylmethyl cellulose (Pharmacoat 603)	40.00	4.000
Flavour	13.00	1.300
Monoammonium glycyrrhizinate	1.00	0.100
Colouring	0.50	0.050
Sugar (milled) to	1000.00	100.000

Syloid ALI is supplied by W R Grace Ltd.
Pharmacoat 603 is supplied by Shinetsu Chemical Co.

The granules were prepared by passing the ingredients and the pharmacoat 603 except the Syloid through a 500 µm (30 mesh) British Standard stainless steel screen and then blending them in a Planetary mixer. The dry powder mix was then stirred at slow speed and dichloromethane added to form a granular mass. The granulated mass then passed through a Fuji Paudal Radial extruder, the extruded product collected, passed through a 1000 µm (16 mesh) screen and dried for 35 minutes at less than 45°C. The dried extrudates were blended with 5% Syloid and stored in sealed containers containing molecular sieve desiccant.

Example 2

Extruded granules of the following composition were prepared :

Ingredients	mg/per Unit Dose	% w/w
Amoxycillin trihydrate B.P. equiv. to amoxycillin	102.5	10.25
Potassium clavulanate equiv. to clavulanic acid	52.5	5.25
Silicic acid, anhydrous (Syloid AL1)	50.0	5.0
Hydroxypropylmethyl cellulose (Pharmacoat 603)	40.0	4.0
Flavour	11.2	1.12
Colouring	0.5	0.05
Sugar (milled) to	1000	100.00

The granules were prepared by passing the ingredients except the Syloid AL1 through the 30# screen, and blending in a planetary mixer. The granulation and drying were carried out as in Example 1, and the Syloid dusted into the final product before putting into suitable containers.

Example 3

The ingredients and process were as for Example 2, but the Syloid was mixed into the wet mass after granulation, but before extrusion and drying.

Example 4

The ingredients were as for Example 2, but the Pharmacoat 603 level was reduced to 1% w/w. All ingredients except the Syloid were screened and blended as in Example 1, and then the powder wetted with dichloromethane to form a workable wet mass. This was extruded and dried as in Example 1, and the Syloid dusted onto the final product.

Example 5

The Pharmacoat 603 in Example 1 was replaced with Kollidon VA64 (r.t.m. B.A.S.F.), a polyvinylpyrrolidone/ polyvinylacetate copolymer, at the 10% w/w level, dissolved in a 1:1 iso-propanol/dichloromethane solvent. This solution was used for the granulation step.

Example 6

The ingredients and process were as for examples 1 and 2, except that the Pharmacoat was excluded from the dry mixing stage. The Pharmacoat was dissolved in a mix of isopropylalcohol and dichloromethane and used to wet mass the dry mix.

Example 7

The ingredients and screening of ingredients were as for Example 1 but the mixing and extruding processes were carried out using a Winkworth Z-Blade Extruder.

The extrudate was then dried as in Example 1, and the Syloid dusted onto the final product.

CLAIMS

(1) An extrudable water dispersible composition comprising amoxycillin trihydrate and potassium clavulanate together with conventional excipients and a non - hygroscopic water soluble binder

(2) A composition as claimed in claim 1 in which the weight ratio of amoxycillin to clavulanic acid is from 12:1 to 2:1

(3) A composition as claimed in claim 1 or claim 2 in which the weight ratio of amoxycillin to clavulanic acid is 8:1, 4:1 or 2:1

(4) A composition as claimed in any of claims 1 to 3 in which the water soluble non-hygroscopic binder is an organic polymer

(5) A composition as claimed in any of claims 1 to 4 in which the water soluble non-hygroscopic binder is hydroxypropylmethylcellulose, polyvinylpyrrolidone/ polyvinylacetate copolymer or hydroxypropylcellulose

(6) A composition as claimed in any of claims 1 to 5 in which the weight of extrudate in a single dose is between 0.25gand 10g.

(7) A composition as claimed in any of claims 1 to 6 in which the weight of extrudate in a single dose is between 0.5 and 5g

(8) A process for the preparation of an extrudable water - dispersible composition as claimed in any of claims 1 to 7 which comprises bringing into association the components of said composition and thereafter extruding the blended mixture

(9) A method of treatment of bacterial infections in man, which method comprises the oral administration to the sufferer of an effective amount of amoxycillin trihydrate and potassium clavulanate in the form of an extrudate claimed in any of claims 1 to 8

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

0080862
Application number

EP 82 30 6274

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Y D	GB - A - 2 005 538 (BEECHAM) * claims * & DE - A - 2 843 318	1-5	A 61 K 31/43 A 61 K 9/00// (A 61 K 31/43 31/42)
Y	EP - A - 0 010 904 (BEECHAM) * page 7, example 2; claims *	1-5	
A	GB - A - 1 532 993 (BEECHAM) * claims *	1,4,5	
P	EP - A - 0 049 061 (BEECHAM) * claims *	1-5	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 K 9/00
31/00
C 07 D 499/00
498/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-8

Claims searched incompletely:

Claims not searched: 9

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (see article 52 (4) of the European Patent Convention).

Place of search	Date of completion of the search	Examiner
The Hague	03-03-1983	CHOULY

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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